Medical and Pediatric Oncology 26:297–304 (1996)

Treatment Outcome and Dose-Response Relationship in Infants Younger Than 1 Year Treated for Retinoblastoma With Primary Irradiation

James Fontanesi, MD, Charles B. Pratt, MD, Larry E. Kun, MD, H. Omar Hustu, MD, Douglas Coffey, MS, and David Meyer, MD

Thirty-three infants (<1 year at diagnosis) were treated for retinoblastoma with primary irradiation at St. Jude Children's Research Hospital (SJCRH) between 1963 and June 1992. Staging of the 44 treated eyes was as follows: Reese-Ellsworth (R-E) Groups I (n = 20), Group II (n = 9), Group III (n = 6), Group IV (n = 2), Group V (n = 7). Irradiation was delivered using either a single anterior field (31 eyes) or lens-sparing techniques (13 eyes). Total doses ranged from 21–45 Gy (median = 36 Gy) in fractions of 150–180 cGy (n = 34) or >180 cGy (n = 10). One child died of metastatic disease at 42 months. Three patients have developed second malignant neoplasms; two have succumbed at 88 and 125 months post-RB diagnosis; the remaining patients are alive at 6–259 months postdiagnosis (median follow-up = 127 months). Local control with irradiation alone and supplemented cryotherapy given within 2 months (n = 2) was maintained in 29 eyes, with no statistical difference seen for total doses ≤36 Gy (21/28 eyes) vs. >36 Gy (8/16). Of 15 eyes that required salvage therapy, tumor control has been maintained in 13. Enucleation was requried for four patients, two with recurrent retinoblastoma and one with a massive retinal hemorrhage, one with a phthisical eye. Cataract formation was documented in 23 eyes (87.5%) treated with anterior field. Three patient treated with lens-sparing techniques developed cataract. At last follow-up, 23 of 30 patients tested (77%) had visual acuity of 20/100 or better. This experience confirms early observations in that doses ≥36 Gy do not appear to improve local control with irradiation alone in infants (<365 days) with retinoblastoma.

Key words: retinoblastoma, pediatric oncology, radiation dose-response

INTRODUCTION

Retinoblastoma (RB) is the most common malignant ocular tumor in children [1]. Its origin and genetic involvement have been well documented [2,3]. RB is known to be radiosensitive, and several studies have reported the curative use of external beam irradiation [4–11] or episcleral plaques [10].

Various external beam techniques have been reported for RB, generally aimed toward irradiating the entire retinal surface [5,6,9–12]. From these reports it is difficult to define a dose-response relationship since these series have used techniques that vary in their adequacy of irradiating the entire retina (anterior field techniques vs. lens-sparing techniques), daily fraction size, and total dose. Additionally, supplemental photocoagulation or cryotherapy is often reported in conjunction with irradiation results, making assessment of local control rates with irradiation alone difficult to interpret. In very young patients, the high frequency of multifocal bilateral disease further complicates any attempts at dose-response analysis because recurrence may be difficult to differentiate from newly developing tumor foci. With the excellent survival rates achieved with modern therapy, it has become increasingly important to assess treatment efficacy in relationship to preservation of vision, development of complications, and evaluation of second malignant neoplasm (SMN) development.

The treatment of small children and infants presents numerous challenges to the radiation oncologist. The frequent need for sedation or general anesthesia, which can cause deviation of gaze from midline, and ocular stabilization devices make the treatment of infants with RB difficult. Additional concerns over long-term sequelae such as bone growth abnormality, cataract formation, and the possibility of SMN development has led to the many

From the Departments of Radiation Oncology (J.F., L.E.K., H.O.H., D.C.) and Hematology-Oncology (C.B.P.), St. Jude Children's Research Hospital, the Vitreoretinal Foundation (D.M.), and the Univeristy of Tennessee, College of Medicine (J.F.), Memphis, Tennessee.

Received September 28, 1993; accepted December 13, 1994.

Address reprint requests to James Fontanesi, M.D., who is now at the Department of Radiation Oncology, Harper Hospital, 3990 John R., Detroit, MI 48201.

TABLE I. Patient Characteristics and Disease Group

Characteristic	Number
Sex	
Male	13
Female	20
Presentation at diagnosis	
Bilateral	n = 30
Unilateral	n = 3
Family history	
Negative	n = 23
Positive	n = 10
Bilateral	n = 8
Unilateral	n = 2
Reese Ellsworth group	
Group I	20
Group II	9
Group III	6
Group IV	2
Group V	7

TABLE II. Radiation Treatment Characteristics

Treatment energies	4 MeV	n = 31
	Co-60	n = 9
	12 MeV electron	n = 4
Total dose[a]	21–45 Gy (med = 36 Gy)	n = 44
	21–36 Gy	n = 28
	37–45 Gy	n = 16
Daily fraction[a]	150–180 cGy	n = 34
	181–275 cGy	n = 10
Treatment technique		
Anterior field	21–36 Gy	n = 22
	37–45 Gy	n = 9
Lens sparing[b]	21–36 Gy	n = 6
	37–45 Gy	n = 7

[a]Defined as the minimum dose within the target volume (globe).
[b]Using lateral or combination anterior and lateral treatment fields.

different treatment techniques and recommendations found in the literature. We report a series of 34 infants treated for RB with primary external beam irradiation, using supplemental therapy as needed. Primary tumor control with irradiation alone and with supplemental cryotherapy (given within 60 days for slowly responding lesions), response to salvage therapy, ocular survival, and visual acuity are reported as outcome measures.

MATERIALS AND METHODS

Between December 31, 1963, and June 1, 1991, 154 children with the diagnosis of RB were seen at St. Jude Children's Research Hospital (SJCRH). Fifty-eight children were diagnosed in infancy (age <365 days), and 33 presented for treatment with irradiation. The remaining 24 children underwent enucleation of the affected eye(s). The majority of the infants had bilateral multifocal disease (n = 30). For these children, radiation therapy was utilized for one eye (n = 19) or both eyes (n = 11). Three infants had unilateral unifocal disease. Patient and disease status characteristics are listed in Table I. Ten patients had family history positive for RB, eight of whom had bilateral disease; three sibling pairs were included in the treatment group. Ten children presented at ages 1–90 days, 10 patients at ages 91–180 days, 6 patients between 181–270 days, and 7 patients 271–365 days of age at diagnosis. A total of 44 eyes were treated with irradiation, which was recommended if following evaluation, the multimodality clinic felt that there was reasonable expectation for visual acuity retention. Indication for irradiation were based on the judgment of the treatment physicians as to suitability of eventual visual outcome, especially in those children with bilateral disease who had enucleation of worst disease eye.

All patients had complete staging studies, comprising clinical history, physical examination, and radiographic studies (including bone scan in all but seven cases). Each child was examined under anesthesia by the same ocular oncologist (D.M.), who prospectively recorded accurate tumor mapping with drawings that included size, site, and number of tumor foci per eye. Photographs were also obtained at the time of diagnosis. Ocular involvement was staged retrospectively by two independent observers using the R-E staging system [7].

Treatment is summarized in Table II. Patients received megavoltage external beam irradiation. Between December 1963 and October 1988, treatment technique and dose were selected by physician preference. Since November 1988, treatment dose was standardized to 36 Gy with technique utilization (anterior vs. lens-sparing) by physician preference. Beam energies included ^{60}Co and 4 MV photons and 12 MeV electrons. Techniques included an anterior field (31 eyes), a lateral field with anterior lens blocked field weighted 5:1 laterally (3 eyes) [13], or opposed lateral fields positioned to avoid divergence anteriorly (10 eyes). Doses, defined as the minimum dose within the target volume of the globe, ranged from 21 to 45 Gy (median = 36 Gy). Dose per fraction was 150–180 cGy for 34 eyes and 180–275 cGy for 10 eyes. Patients were treated either 4 or 5 days a week. Each patient was positioned following induction of general anesthesia or sedation and monitored. At completion of irradiation, two eyes required supplemental cryotherapy for disease that had not shown prompt regression.

Follow-up has been maintained for all patients and ranges from 6 to 259 months (median = 127 months). Results of recent visual acuity testing are available for 30 children.

RESULTS

Patient Survival

Thirty of 33 patients remain alive between 6 months and 259 months postdiagnosis (median = 127 months).

Three patients have died. One patient developed metastatic RB at 17 months and died at 42 months with local control of the ocular disease. Two/three patients who have developed second malignant neoplasm have died. Both of these patients presented with bilateral familial RB (siblings with RB). One developed osteogenic sarcoma (OS) within the treatment field. This patient received 32 Gy with anterior field and was noted to have recurrent disease that received additional irradiation using anterior and lateral field arrangement. The additional 34 Gy was delivered 7 months following completion of the initial irradiation. This patient succumbed 88 months following diagnosis of RB. The second patient who succumbed due to SMN was noted to have a Ewings sarcoma of the calcaneus with bone metastasis noted at diagnosis. This patient succumbed 14 months post-SMN diagnosis and 125 months post RB diagnosis.

Local Survival

Local control is defined as nonprogression of RB following use of primary irradiation; eventual local control includes those patients with evidence of progression of old RB sites or development of new RB sites postirradiation who were successfully salvaged. Overall, 40/44 eyes remain intact. Each patient with unilateral disease presentation has maintained ocular survival with 37/41 eyes in patients with bilateral presentation maintaining ocular use.

Local control following irradiation alone was documented in 29 eyes (21/28 receiving ≤36 Gy and 8/16 recurring >36 Gy). Two of these eyes required supplemental cryotherapy within 60 days of completion of irradiation for incompletely responding RB. Fifteen patients required retreatment for recurrent RB between 5–69 months post-RB diagnosis (median = 17 months).

Four patient treated for recurrent RB required enucleation postsalvage. Two of four eyes had persistent RB that were unresponsive to salvage attempts. The remaining two eyes had no pathologic evidence of RB at the time of enucleation; however, in one eye vitreous hemmorage occurred that did not allow for subsequent adaquate examination. The second case developed a painful phthisical eye that was unresponsive to medical management (Table III.)

Treatment Results by Dose

Dose <36 Gy. Twenty-eight eyes were treated with total doses that ranged from 21 to 36 Gy. Twenty (71.4%) required no further therapy (Table IV). One patient received supplemental cryotherapy at 2 months postexternal beam irradiation (dose = 22.5 Gy) and remains locally controlled. The overall rate of primary disease control is 75% (21/28) for all stages.

Seven eyes required salvage therapy >2 months postirradiation. Three of seven received total dose ≤30 Gy via anterior field. The remaining eyes received 36 Gy using lens-sparing technique. Time to progression, recurrent site, retreatment, and results are found on Table V. Three of these patients eventually required enucleation; two for tumor progression and one for phthisical eye (Table IV).

Overall, 25/28 (89%) eyes remain intact following initial irradiation (n = 20), supplemental cryotherapy (n = 1) or salvage therapy (n = 4) with ≤36 Gy.

Dose >36 Gy. Sixteen eyes were treated with total doses that ranged from 37 to 45 Gy (median = 42.5 Gy). Eight (50%) required no further therapy (Table IV). One patient required supplemental cryotherapy 2 months following irradiation and remains in local control at 239 months. The rate of primary disease control is 9/16 (56%) for all stages.

Eight eyes required salvage therapy 5–48 months postirradiation. Initial irradiation dose ranged from 41.4 to 45 Gy. Characteristics of these local failures are found in Table V. One patient required enucleation following successful salvage with cryotherapy and re-irradiation secondary to recurrent vitreous hemorrhage. The remaining 15 eyes (94%) remain intact.

STATISTICAL EVALUATION

Using the Fischer exact test, we were able to document equal distribution of the number of patients within RE Groups I–V ($P = .51$) and receiving either anterior or lens- sparing technique ($P = .17$). The log rank test was utilized to evaluate impact of dose (≤36 Gy, >36 Gy) on eventual local control. No advantage was documented for patients receiving >36 Gy when compared to the lesser dose group ($P = .066$). There was no statistical improvement in local control for treatment technique (anterior field compared to lateral lens-sparing; $P = .23$) or within the R-E groups (I/II compared with III and IV/V; $P = .32$) when evaluated with log rank analysis.

Complications

Clinically significant posterior subcapsular cataracts developed 12–49 months after irradiation in 23/27 eyes treated with anterior fields (total doses of 21-44 Gy). Subsequent lensectomy was well tolerated, with little morbidity [14]. There has been one eye that developed clinically significant cataract among 17 treated with lens-sparing techniques.

Visual acuity at last follow-up (minimum 24 month postirradiation; median = 37 months) was 20/100 or better with correction in 23 of 30 patients tested (77%). The remaining patients have finger-counting ability at 4–6 feet with correction.

All patients who received radiation doses >26 Gy (n = 25) have some degree of facial asymmetry, which is

TABLE III. Enucleation: Patient Characteristics and Therapy

Pt	Age @ Dx (days)	R-E group (enucleated globe) OD	OS	Family history	Presentation	Irradiation Date	Dose (Gy)	Field[a]	Machine[b]	Progression TTP[c] (months)	Site (ant/post)[d]	Type	Date enuc	Path/F/U
1	270		VB	+	Unilateral	10/81	23	A	4	10	post	old	10/82	+RB: Irradiation given as pre-operative dose; patient had >90% tumor clearance at 3 mos. Progression at 10 mos. NED 132 mos.
2	150	IIIA	IIB	—	Bilateral	1/79	42	A	4	10	post	old	8/82	−RB: Pt received cryotx 11/79, then re-irradiation 8/80. Developed vit[e] hemorrhage. NED 165 mos.
3	60	(VA)	IIA	—	Bilateral	2/90	36	L	4	14	ant	new	7/91	+RB; massive. Pt treated with I-125 at initial recur. Developed anterior chamber disease. NED 32 mos.
4	60	(IIIA)	IIIA	—	Bilateral	10/89	36	L	4	10	ant	old	10/90	−RB: Pt re-irradiated 8/90 with 39 Gy anterior field. Phthisical/painful eye 9/90. NED 38 mos.

[a]A = anterior field; L = lateral lens sparing field.
[b]4 = 4 MeV photon.
[c]Time to progression. [d]Ant = anterior to equator; post = posterior to equator.
[e]Vitreous.

TABLE IV. Response to Irradiation (including supplemental cryotherapy within 60 days)

	Local control			
	≤36 Gy		>36 Gy	
	Anterior	Lens sparing	Anterior	Lens sparing
Re group				
I	9/11	2/3	1/2	3/4
II	4/4	—	2[a]	
III	2/2	—	0/1	1/3
IV	2[a]	—	—	—
V	2/3	0/3	1/1	—
	Local failure (treatment dose)			
	≤36 Gy		>36 Gy	
	Anterior	Lens sparing	Anterior	Lens sparing
Re group				
I	22.5,[b] 30	36	43.6	45
II	—	—	40, 42, 43	—
III	—		45	41.4, 41.4
IV	—	—	—	—
V	23	36, 36, 36	—	—

[a]Includes one patient with cryotherapy within 2 months.
[b]Includes one patient with preoperative dose.

cosmetically significant in only three cases (all treated with lateral field techniques to doses of 30, 35, and 36 Gy).

There has been a single case of neovascular glaucoma secondary to irradiation. This patient presented at 8 months of age with bilateral RB and underwent enucleation of the more involved eye. The patient then received 42.5 Gy in 16 fractions over 22 days by anterior field technique. Follow-up pressure measurements over the next 26 months documented changes consistent with radiation-induced neovascular glaucoma. It is possible that the high daily fractionation scheme used was responsible for development of neo-vascular glaucoma.

There were three cases of radiation-induced keratitis, all in patients with bilateral RB after enucleation of the worst eye. These infants were treated via anterior field to total doses of 40.1, 42, and 44 Gy. Each patient had resolution of symptoms within 6 months with conservative therapy. No patient had documented lacrimal duct occlusion secondary to irradiation.

DISCUSSION

Beginning with Hilgartner's first reported use in 1903, irradiation has been used in the management of RB [15]. However, it is difficult to determine dose response and outcome related to irradiation alone since many series have reported widely varying total doses, techniques, and inconsistent use of supplemental cryotherapy for incompletely responding tumors. Identifying radiation parameters is of vital importance as we struggle with the issue of high local control rates while attempting to diminish side effects, especially in a population of very young children with high predilection for development of SMNs both inside and outside the irradiated field.

Stallard proposed as early as 1953 that 35 Gy in 7 days with Co^{60} plaque was sufficient for eradication of RB cells [11]. This was verified by Cassady et al. [5], who could not demonstrate increased local control with doses beyond 36 Gy. However, it was suggested that increased dose might improve the poor prognosis in patients with residual or recurrent disease [5]. This study and most subsequent studies utilized the R-E [7] staging system that was thought accurately to predict visual acuity success from irradiation but could not predict outcome with respect to extraocular involvement. This staging system has been questioned, particularly the role that vitreous seeding (RE Group VB) plays in eventual visual outcome.

Despite this information, there has been a gradual increase in the total dose recommended for RB despite a lack of clear evidence of increased local control to date. This has been demonstrated by several series including Egbert et al. [6], who reported on 28 children treated between 1956 and 1974. In this series with follow-up as long as 21 years, 16 (42%) eyes required enucleation for recurrent tumor, neovascular glaucoma, or inability to observe the tumor through opaque media following dose up to 60 Gy. This is also the experience reported by Foote et al. [6] in which 14/25 (56%) patients required additional treatment following doses between 39 and 51 Gy. They reported that 45 Gy appeared adequate for lesion

TABLE V. Recurrent Retinoblastoma Characteristics (excluding patients receiving supplemental cryotherapy within 60 days of completion of irradiation)

Pt.#	Age @ dx (mos)	Presentation[a]	Family history	RE (of local failure site) OD	RE (of local failure site) OS	Irradiation Date	Irradiation Dose (Gy)	Field[b]	Machine	Failure TTP[c] (mos) from dx	Failure Site	Failure Type	Treatment	Complication (months to diagnosis)[d]	Status (mos) from dx/mos from salvage
1	9	U	+		VB	10/81	23	ANT	4	10	Posterior	Old	Enucleation 10/82[e]	—	132+/122+
2	12	Bil	—	IB		12/81	22.5	ANT	4	7	Posterior	Old/new	Cryotherapy 2/79	CAT (24)	130/123+
3	9	Bil	—	IIB		8/77	43	ANT	4	17	Anterior	New	Cryotherapy 1/79	CAT (27)	182/165+
4	3	Bil	—		IIB	12/72	40	ANT	CO	11	Posterior	Old	Cryotherapy 10/73	Keratitis (37)	238/227+
5	3	Bil	—	VA		7/83	36	A/L	4	14	Anterior	New	Cryotherapy 9/84	CAT (12)	111/94+
											"	Old	11/84	CAT (42)	
											"	"	1/85		
											"	"	6/85		
6	5	Bil	—		IIB	1/79	42	ANT	4	10	Posterior	Old	Cryotherapy 11/79 Re-irradiation 8/80 Enucleation 8/82[f]		165/122+
7	11	Bil	—	IB		4/71	43.6	ANT	CO	10	Posterior	Old	Cryotherapy 2/72	CAT (24)	258/248+
8	7	U	—	IA		1/83	36	LAT	4	69	Posterior	New	I-125[g] 10/88		117/60+
9	3	Bil	+	IA		10/88	45	LAT	4	14	Posterior	Old	I-125[g] 12/89	CAT (30)	48/34+
10	7	Bil	—	IIIA		6/90	41.4	LAT	4	5	Anterior	New	Cryotherapy 9/90		28/17+
					IIIA	6/90	41.4	LAT	4		Anterior	Old	I-125[g] 5/91		
											Anterior	New	Cryotherapy		
											Anterior	Old	I-125[g] 1/91		28/22+
11	<1	Bil	+		IB	9/77	30	ANT	CO	17	Posterior	Old/new	Cryotherapy 2/79	CAT (46)	158/141+
12	6	Bil	+	IIIB		7/85	45	ANT	4	48	Posterior	Old	I-125[g] 7/89	CAT (49)	169 SMN
13	2	Bil	—	VA		2/90	36	LAT	4	14	Anterior	New	Enucleation 7/91		32/15+
14	2	Bil	—	VA		10/89	36	LAT	4	10	Anterior	Old	Re-irradiation 8/90 Enucleation 10/90[h]		36/24+

[a]Unilateral; bilateral.
[b]ANT = anterior; A/L = anterior lateral; LAT = lateral.
[c]Time to progression.
[d]CAT = cataract.
[e]Tumor progression.
[f]Vitreous hemorrhage.
[g]40 Gy to tumor apex (via ultrasound) in 96 hours.
[h]phthisical eye.

<10 disc diameters, but reported that their use of lateral anterior segment sparing technique had a high risk of anterior retinal recurrence. In addition, they reported 4/14 (28%) developed posterior subcapsular cataract (PSC) using lens-sparing technique. This combination of problems (i.e., anterior tumor relapse and PSC development) is not unique to the previous series but has also been reported by Salmonsen [17], Thompson [18], and even Schipper [9]. This series is unable to document statistical improvement in local control following irradiation alone with doses >36 Gy. The overall local control rate of 67% (30/45) with supplemental cryotherapy is similar to the cited series.

We are unable to substantiate that increased dose of irradiation has improved local control rates; however, it has been associated with increased complications. Abramson reported increasing complications (ranging from 10% to 100%) with increasing total doses [19]. It is interesting that whereas cataracts, neovascular glaucoma, and other ocular complications have been widely reported in the literature, little has been mentioned of bony abnormalities following irradiation. In our experience, all children <1 year old who received >30 Gy using lens-sparing technique experience some facial asymmetry. The only three patients with cosmetically significant asymmetry in our series were those treated with lateral field receiving between 36 and 45 Gy. Additionally, the sole case of radiation induced neovascular glaucoma may be secondary to the high daily fractionation (226cGy/fraction) utilized.

A majority of patients treated with anterior field for RB will develop PSC; it has also been reported in up to 30% of patients treated with lens-sparing techniques. It is not surprising that we report 87.5% incident of clinically significant PSC in patients treated with anterior fields. However, it has been demonstrated by Brooks [14] that lensectomy is a safe procedure in these patients when there is no evidence of ocular disease. Additionally, 23/30 tested patients (include lensectomy patients) had visual acuity of 20/100 or better with correction. We also have not found clinically significant PSC prior to 16 months postirradiation, thereby substantiating onset long enough so as not to allow development of deprivationed amblyopia.

The use of irradiation in children with potential for *long-term* survival has raised concerns regarding the induction of second malignancies, especially in those patients with the hereditary form of RB. Series have suggested up to 90% cumulative incidence of SMN at 30 years following initial diagnosis in survivors of RB [20,21]. In our series with a median follow-up of 127 months, three patients have developed SMN. We speculate that the lower doses used in this series and the absence of orthovoltage irradiation may have resulted in the comparative low incidence of SMN [6]. Although longer follow-up is needed to substantiate this finding, the median follow-up at >10 years suggests the observation may have some validity.

CONCLUSIONS

Based on the results of this series, which has demonstrated excellent ultimate disease control and ocular preservation, we continue to recommend use of 36 Gy (using conventional fractionation) and judicious use of supplemental cryotherapy in conjunction with close observation for patients <1 year old with early stage RB.

ACKNOWLEDGMENTS

The authors thank Sandra Gaither and Theresa Lay for manuscript preparation. This work was supported in part by Cancer Center Support CORE grant CA 21765 and the American Lebanese Syrian Associated Charities (ALSAC).

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